

From: Krissy.Carrington@sanofipasteur.com
To: [Rivers, Katie](#)
Cc: [Hoffman, Kelsy](#); [Chattopadhyay, Rana](#)
Subject: RE: Request for Additional Information for STN125563/0
Date: Monday, July 27, 2015 1:42:08 PM

Dear Katie

I acknowledge the receipt of this IR letter. Kind regards,
Krissy

From: Rivers, Katie [mailto:Katie.Rivers@fda.hhs.gov]
Sent: Monday, July 27, 2015 1:23 PM
To: Carrington, Krissy (sanofi pasteur)
Cc: Hoffman, Kelsy; Chattopadhyay, Rana
Subject: Request for Additional Information for STN125563/0

Dear Ms. Carrington,

We have reviewed your May 28, 2015 and June 05, 2015 amendments to STN125563/0 provided in response to our April 17, 2015 information request (IR) and have the following comments and requests for additional information:

1. You have stated in your response to Question 15c of the IR dated 17 April 2015 that stability studies of PR5I Final Bulk Product using (b) (4) are not warranted. We do not concur with your response. Please provide stability data for Final Bulk Product stored in containers used in routine manufacturing to support your proposed expiry of (b) (4) for PR5I Final Bulk Product. Alternatively, please commit to provide these data post approval.
2. In your response to Question 4 of the IR dated 17 April 2015, you propose a (b) (4) specification of (b) (4) for release and (b) (4) for stability. You propose two sets of specifications based on an (b) (4) trending that you have observed over time. The stability data presented do not support an (b) (4) trending for (b) (4). Your proposed stability specification is based on statistical analysis of (b) (4) test results from stability monitoring up to and including the 42 month time-point. We do not concur with your proposed stability specification. Please revise your stability specification for (b) (4) to be the same as that proposed for your release specification.
3. In your response to Question 3c of the IR dated 17 April 2015, you state that the data provided in Table 1 in conjunction with the satisfactory batch release results support the (b) (4) conditions for PRP-OMPC Bulk. We do not concur. You are proposing a (b) (4) for the PRP-OMPC bulk (b) (4). The data provided support a (b) (4). Please provide data using the current manufacturing process to support the entire range of the proposed (b) (4) time. Alternatively, please commit to provide these data post approval.
4. In your response to Question 23 of the IR dated 17 April 2015, you state that it is the company's position that (b) (4) testing is not required on the PR5I (b) (4) Product since (b) (4) testing is performed at various stages of manufacturing and pyrogen testing

is conducted on the PR5I Filled Product. We note that you reference the PR5I End of Phase 2 / Pre-Phase 3 CMC Meeting of 28 March 2007 in which we recommended that you evaluate pyrogenicity at release and expiry and endotoxin content at intermediate time-points. Please note that these recommendations were in response to your proposed Phase III release and stability testing plan. The pyrogen test and endotoxin test will both provide assurance of safety and consistency of manufacture since LPS is known to be associated with the OMPC component of your vaccine. Therefore, we ask that you please add an endotoxin test for both release and stability testing of PR5I Filled Product and include an endotoxin specification to reflect manufacturing data. Alternatively, please commit to add this test post approval.

5. In your response to Question 13c of the IR dated 17 April 2015, you state that the reference standard used for (b) (4) and Identity of PRP-OMPC will be re-evaluated for extension of dating by evaluating the (b) (4) for any potential trends. You have not provided comments to all of our concerns raised in Question 13c. Please provide detailed procedures on how the reference standard will be re-evaluated for extension of dating. Please provide limits on the number of times a reference standard can be re-evaluated and expiry extended. Since your procedure allows for extension of dating beyond the approved hold time of the PRP-OMPC Conjugate lot, please describe how the reference standard is monitored to ensure that it does not deteriorate in quality beyond the expected shelf life of the Conjugate lot.
6. In your response to Question 14b of the IR dated 17 April 2015, you provide your procedure on how the reference standard used for PRP Content and (b) (4) PRP-OMPC will be re-evaluated for extension of dating. You have not provided comments to all of our concerns raised in Question 14c. Please provide limits on the number of times a reference standard can be re-evaluated and expiry extended. Since your procedure allows for extension of dating beyond the approved hold time of the PRP lot, please describe how the reference standard is monitored to ensure that it does not deteriorate in quality beyond the expected shelf life of the PRP lot.
7. In your responses to Questions 4, 5, 6, 7, and 8 of the IR dated 17 April 2015, you have committed to re-evaluate the specification limits for (b) (4) (b) (4) (b) (4) PRP-OMPC, (b) (4) of PRP-OMPC, PRP Content, and (b) (4) respectively, once data are collected from approximately (b) (4) PR5I vaccine lots, or earlier if warranted due to data trending. Please confirm that you plan to re-evaluate your specifications by using the tolerance intervals with 99% coverage and 95% confidence.

Please let me know if you have any questions.

Thank you,
Katie

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